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Evaluating biomaterials & implanted devices

EDITORIAL

Editorial to ``Evaluating biomaterials and implanted devices''

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Editorial 'Evaluating biomaterials and implanted devices'

The use of biomaterials and implanted devices has grown very rapidly in the last decades. Despite the fact that biomaterials have been used for healthcare applications since ancient times, the recent development of new and more versatile materials has expanded their potential clinical applications

Roberto Gaetani, PhD is a Research Scientist at the Department of Bioengineering at the University of California, San Diego. He studied biotechnology at the Sapienza University of Rome followed by a Master in Medical and Molecular Biotechnology and a PhD in Pasteurian Science at the same institution. In 2013 he worked at the Department of Experimental Cardiology at the University Medical Center in Utrecht as a post-doc until he joined the Department of Bioengineering at the University of California, San Diego to complete his postdoctoral studies. He became Research Scientist at the same Department in 2015 and co-director of the summer program in Biomaterials in 2016. He has >25 peer-reviewed publications and has participated in collaborative research projects with academic laboratories in Europe and the US. Dr. Gaetani research area of interest focuses on the development and use of tissue-derived biomaterials in combination with stem cells for the generation of hybrid scaffolds or as a platform for biologics delivery, such as exosomes and microRNA, for myocardial infarction repair. He also studies how tissue-specific extracellular matrix molecules influence the phenotype and functionality of the cultured cells with particular emphasis on the development of new functional biomaterials for cardiac and diabetes tissue engineering applications.

Karen L. Christman, PhD is a Professor in the Department of Bioengineering and the Associate Dean for Students in the Jacobs School of Engineering at UC San Diego. She received her B.S. in Biomedical Engineering from Northwestern University in 2000 and her Ph.D. from the University of California San Francisco and Berkeley Joint Bioengineering Graduate Group in 2003, where she examined *in situ* approaches to myocardial tissue engineering. She was also a NIH postdoctoral fellow at the University of California, Los Angeles in the fields of polymer chemistry and nanotechnology. Dr. Christman joined the Department of Bioengineering in 2007 and is a member of the Institute of Engineering in Medicine at the University of California, San Diego. Her lab, which is housed in the Sanford Consortium for Regenerative Medicine, focuses on developing novel biomaterials for tissue engineering and regenerative medicine applications, and has a strong translational focus with the main goal of developing minimally invasive therapies for cardiovascular disease. Dr. Christman is a fellow of the American Heart Association and the American Institute for Medical and Biological Engineering, and has received several awards including the NIH Director's New Innovator and Transformative Research Awards, the Wallace H. Coulter Foundation Early Career Translational Research Award, the American Heart Association Western States Innovative Sciences Award, and the Tissue Engineering and Regenerative Medicine Society's Young Investigator Award. Dr. Christman is also co-founder of Ventrix, Inc., which is in clinical trials with the cardiac extracellular matrix hydrogel technology developed in her lab at UC San Diego.

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and revolutionized the areas of biology, bioengineering and tissue engineering for the development of new therapeutic approaches aimed at restoring lost functionality of the damaged tissues. Biomaterials are now used for a variety of tissue engineering applications including acellular scaffolds alone, either with pro regenerative capabilities or as a tissue filler or substitute. They can also be used as a platform for prolonged delivery of cells, drugs or other therapeutic biologics, or for the in vitro generation of tissues and organs. Together with the development of new types of biomaterials and potential therapeutic applications, the sector market value has risen consistently over the years, which is indicative of the potential of the field. A recent research report on the Global Biomaterials Market by Market Research Future predicts that the global biomaterials market for diagnosis and treatment is projected to reach USD 149.17 Billion by 2021 from an estimated USD 70.90 Billion in 2016, at a compound annual growth rate (CAGR) of 16.0%. Among the different fields of applications, the cardiovascular market is expected to account for the largest share of the biomaterials market. This is not surprising considering that, according to the World Health Organization, cardiovascular diseases represent the leading causes of death globally.

Together with the generation of new biomaterials, the development of new preclinical models that better recapitulate the complexity of human disease has grown exponentially. These models are fundamental in order to evaluate the safety and efficacy of the newly developed products and should recapitulate as close as possible the complex conditions that occur in human diseases. Moreover, since many biomaterials and implanted devices are often composed of synthetic materials, another fundamental aspect of evaluating safety is their biocompatibility, and the immune response triggered when transplanted in vivo.

In this issue of DDT, we addressed the recent advances that have been made in animal models to test biomaterials and implanted devices for cardiovascular applications including current strategies and animal models to evaluate the immune response of the transplanted applications.

The first part of the issue focuses on the evaluation of the host response to implanted material and devices. In the first manuscript by J. L. Dziki and S. F. Badylak, the authors covered the recent developments in modeling immune cell-material interactions and addressed the importance of the immune response to biomaterials, both in vitro and in vivo, with emphasis on tissue-derived decellularized biomaterials. The interactions between implanted materials and host immune cells could strongly influence either a pro-fibrotic or a pro-regenerative response of the host tissue and ultimately the therapeutic efficacy of the implanted tissue or device. As the authors point out, in vitro models cannot recapitulate the complex immune response that occurs in vivo, but have the advantage to evaluate the effects of a material to a specific cell type and at single cell level. On the other end, in vivo models recapitulate better the complex response, including all different cell types involved in the inflammatory response. They can also be used to evaluate systemic effects of the material and used for measurement of temporal changes of various factors such as cytokines, pH and other potential biomarkers. In the second manuscript of the issue, L. S. Saleh and S. J. Bryant also addressed the biomaterial- immune cell response with particular emphasis to the foreign body reaction (FBR) which occurs ubiquitously to all non-biological materials implanted in vivo. The authors described the most promising in vitro models to study FBR reaction and in particular to evaluate macrophage adhesion, polarization, and fusion, which are often critical components of the FBR response. Moreover, the authors also covered advantages and differences among the different animal models such as mice, both wild-type and transgenic, and non-human primate, providing valuable insight into all the key cellular players and their phenotype in the generation of the FBR to the implanted material. However, the many differences in the immune response among the different animal species used in pre-clinical evaluations and the human immune response are still a major limitation in this type of studies. A possible solution to this issue has now been proposed and involves the use of humanized mouse models, which was evaluated in the third paper of this issue by R. M. Wang et al. In the manuscript the authors covered the recent advancement in generating humanized mouse models that closely recapitulate the human immune system. This approach uses immunodeficient mice in which the immune component has been replaced with human tissue and cells thus generating mice with a reconstituted human-derived immune system. In particular, the authors evaluated and demonstrated that this animal model could also be used to assess the immune response to biomaterials, which represents a valid tool in the prediction of immune cell- biomaterial interaction thus being potentially able to anticipate unexpected cellular responses to biomaterial-based therapies in human patients.

The second part of the issue covers recently developed animal models for different cardiovascular applications, spanning from vascular stenting and grafts to heart valves and mechanical circulatory support devices. The manuscript by L. E. Leigh Perkins offers a valuable overview of all models that are currently used to evaluate the efficacy of newly developed vascular stents including rodents, rabbits, dogs, sheep, swine, and non-human primates. The authors addressed advantages and disadvantages of each model to provide insight into the pathophysiology of vessel healing and restenosis and to assess the potential efficacy of a stent at improving specific clinical outcomes and evaluate the safety of the application for a specified clinical use. In the following article S. Row et al. evaluated the different animal models

used for testing vascular grafts. The authors pointed out that many applications have often used healthy wild-type rodents or large animal models. Despite being very valuable, these models lack the diseased vascular state that is often present in humans and therefore failed to represent a valid tool in testing the efficacy of the transplanted vascular grafts. The use of transgenic mice may partly overcome this limitation. However, the use of large animal models with specific pathologies or age may be more representative of the human disease and should be used for the final evaluation of efficacy before testing in clinical trials. The sixth manuscript by T. Miyamoto et al. covered the animal models used for the development and validation of mechanical circulatory support (MCS) devices that are widely used to treat patients with heart failure. The authors focused on the current debates on what might be the ideal surgical approach to evaluating MCS devices in large animals, the hemodynamic and laboratory differences between large animals and humans, heart failure models using large animals, and study designs for developing new long-term MCS devices. In the last manuscript of the issue, A. Kheradvar et al. evaluated recent advancements in animal models for heart valve research and development. Heart valve disease is a progressive disease which leads to death if untreated, with the only current option being heart valve replacement. The authors described the two main areas of research in this field, which aim either to understand the underlying mechanisms for heart valve disease or the generation of new replacement options for a diseased valve. The manuscript described the state-of-the-art of the different animal models that are currently being used in the field with emphasis on the advantages and disadvantages of each model. If small transgenic rodents are a valuable tool to study the underlining mechanisms involved in the disease development, the large animal models are currently the best option for testing newly developed strategies due to their similarities with humans.

In conclusion, this special issue offers a state-of-the-art overview of the main aspects of the current research with biomaterials in cardiovascular applications ranging from the host–material interaction to the different animal models currently used to develop and test the efficacy of new biomaterial-based approaches for different cardiovascular applications. Knowing the limitations and advantages of all the currently available animal models is fundamental for biomaterials development, and we believe that this special issue provides a valuable overview of the many aspects that should be considered in developing and testing biomaterial-based therapeutic products for cardiovascular applications.